A systematic search for DNA methyltransferase polymorphisms reveals a rare DNMT3L variant associated with subtelomeric hypomethylation.

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Public Summary:

Scientific Abstract:
Causes underlying inter-individual variations in DNA methylation profiles among normal healthy populations are not thoroughly understood. To investigate the contribution of genetic variation in DNA methyltransferase (DNMT) genes to such epigenetic variation, we performed a systematic search for polymorphisms in all known human DNMT genes [DNMT1, DNMT3A, DNMT3B, DNMT3L and DNMT2 (TRDMT1)] in 192 healthy males and females. One hundred and eleven different polymorphisms were detected. Of these, 24 were located in coding regions and 10 resulted in an amino acid change that may affect the corresponding DNMT protein structure or function. Association analysis between all major polymorphisms (frequency > 1%) and quantitative DNA methylation profiles did not return significant results after correction for multiple testing. Polymorphisms leading to an amino acid change were further investigated for changes in global DNA methylation by differential methylation hybridization. This analysis revealed that a rare change at DNMT3L (R271Q) was associated with significant DNA hypomethylation. Biochemical characterization confirmed that DNMT3L(R271Q) is impaired in its ability to stimulate de novo DNA methylation by DNMT3A. Methylated DNA immunoprecipitation based analysis using CpG island microarrays revealed that the hypomethylation in this sample preferentially clustered to subtelomeric genomic regions with affected loci corresponding to a subset of repetitive CpG islands with low predicted promoter potential located outside of genes.